REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Claims 7-17 and 20-32 are currently pending. The amendments to the claims point out more particularly and claim more distinctly the subject matter of Applicants' invention. No prohibited new matter has been introduced by this Amendment. Applicants reserve the right to pursue in a division or continuation application any subject matter canceled by way of this Amendment without prejudice or disclaimer.

Specifically, the claims have been amended to make claims 23-27 and 29 dependent off of claim 20 as claim 22 is canceled herein. Claim 7 has been amended to recite the preamble as an element of the main body of the claim. Thus, the basis for the amendments to the claims may be found throughout the specification and claims as filed.

I. OATH/DECLARATION

The Declaration stands objected to as purportedly not identifying the application by number and filing date, and not identifying the citizenship and post office addresses of the inventors. Applicants respectfully submit that a substitute Declaration providing all of the above information will follow shortly with a supplemental Reply and Amendment.

II. OBJECTIONS TO THE SPECIFICATION/DRAWINGS

The drawings stand objected to for purportedly failing to show proper correspondence with the Brief Description of the Drawings in the specification. The specification has been amended to described each panel of Figures 1-3. All drawings are attached herewith. Thus, Applicants submit that this rejection has been obviated.

III. CLAIM OBJECTIONS

Claim 22 is objected to for purportedly being a duplicate of claim 20. Claim 22 has been deleted by way of the present Amendment. Thus, Applicants submit that this rejection is moot.

IV. CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 7-17 and 20-32 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for promoting skin wound healing in a diabetic mouse model by surface administering a nucleic acid expressing the tissue factor, purportedly does not reasonably provide enablement for enhancing blood vessel formation in any location of the subject, or for treatment of diseases in human by any routes.

Applicants respectfully submit that the specification, in combination with what was known to the skilled artisan at the time this invention was filed (August 25, 2002), provides enablement commensurate with the scope of the claims.

Page 4 of the Office Action states that the "state of the art is not well developed and is highly unpredictable". Applicants submit that the state of the art should be seen in relation to the kind and objective of the particular method to be applied. There are areas and examples in the field of gene therapy where the state of the art is advanced and a high degree of predictability is achieved. High degrees of predictability are especially common in areas of research where known, physiological processes are addressed. Even in the other areas state of the art has made dramatic progress. The Office Action cites Verma *et al.* (Nat. 1997, Sep, 339,239-242) as disclosing the problems associated with gene therapy in general. However, Applicants submit that in the same cited article that "in the not too distant future" gene therapy will become as routine a practice as heart transplantations are today". This conclusion for gene therapy in general shows that the author is confident that experts in the field were and are able to bring current knowledge (of 1997 and before) to a clinical success by following obvious straight forward approaches. The very same confidence has been shared by many experts in the field of gene therapy. Around the time of the publication of Verma *et al.* (1997), ample applied research and engineering was being carried out considering different promising approaches. These new approaches were possible after several years of disappointing results (as described by Verma *et al.*) teaching the experienced gene therapy practitioner how to use or adapt the method for future use. It is a typical phenomena for emerging technologies that initial failures can provide clear strategies to a successful use of such methods, even though not every attempt is successful.

With regard to the present invention, one important aspect the applied gene therapy method for the induction of blood vessel formation and/or of wound healing for therapy, should be considered. Disadvantages of previous applications that caused failures, unpredictability and diffuse outcomes were avoided *a priori* or even turned into advantages, remaining in the area of well established knowledge as to technical aspects and achievable therapeutic outcomes. Thus, Applicants submit that the skilled artisan would know how to achieve the same therapeutic outcomes disclosed by the present invention and covered by the claims.

With regard to the present invention, disadvantages of previous applications that caused failures and unpredictable outcomes were avoided by the following measures:

- by choosing a topical/local administration and action of the gene product at the site of administration rather than systemic administration and/or need of the vector to cross barriers other than the cell membrane;
- by easy physical targeting of the gene therapy product by medical devices;
- by overexpressing an endogenous highly conserved gene leather than replacing or adding a new gene and thus avoiding technical difficulties as well as an immune response against the gene product;
- by accepting or even demanding a timely and locally limited expression of the therapeutic gene;

- by limiting the therapeutic objective of the method to the initiation of a physiological process where the process itself is still functional but the initiation fails / has failed in the particular disease;
- and by reducing or even avoiding Immune responses against the vector by using non-viral vectors and/or by limiting the application to one or only few administrations.

Furthermore, the case of widely used vaccination by gene transfer (where even immune response against the gene product is demanded) gene therapy for the induction or the enhancement of a blocked or weakened physiological process has become an easy to apply method for gene therapy experts. Among these physiological processes, activation of the immune system and angiogenesis are the most advanced and successful targets for induction by a gene therapy product. For these types of applications, experts were and are no longer limited by technical aspects new findings focus on a gone of interest and respective diseases.

Administration/Targeting

With regard to the diseases mentioned in claims 30-32, any gene therapy product can be applied by standard methods using physical targeting with technical devices already in use (*i.e.*, syringes for direct injection, catheters for intravascular administration, endoscopic devices or particular capsules designed with release-switches for targeted administration in the gastrointestinal tract). This is shown by examples from the literature where these methods have been used for the application of gene therapy products In diseases mentioned in claims 30-32. For

example, Folkman (*Nature Medicine* (1996) 2:167-168) showed that intramuscular gene transfer of naked plasmid DNA encoding VEGF into ischemic limbs, reduced pain and increased healing of ischemic ulcers. In addition there are devices known to target the release of drugs to certain sites of the gastro-intestinal tracts by imaging techniques to localize the device and magnetic stimulation of release. Thus, the skilled artisan knew how to administer gone therapy products to target sites other than the body surface by means of application of standard devices already in use. Success can be achieved based an the experience gained by previous failures in gene therapy.

Induction of a physiological process for therapy in a variety of diseases

In all diseases the events can and most likely do occur clinically silent as can also be expected even for healthy subjects. In healthy subjects and in silent cases physiological processes do often help to circumvent or to countermeasure the pathophysiological process which otherwise would lead to the event. It is a widely known principle of physiology that pro- and anti-processes are in balance in health, and that a temporary Imbalance leading to acute and subchronic, sometimes clinically silent states is turned back to balance often by the very same inductors. Clinically apparent events often occur after a subchronic or chronic disturbance of this regulation by exhausted and otherwise impaired processes. This principle can be expected for the diseases mentioned in claims 30-32 where blood vessel formation and/or wound healing is impaired after a history of disturbed but still somehow functional angiogenesis and wound healing. Thus, ulcer healing does

occur in diabetic patients as well as in patients with inflammatory bowel disease. Blood vessel formation does occur in patients with occlusive vascular diseases, thrombosis etc. Thus in cases where such a process does no longer occur or is too weak, induction or enhancement; of this physiological process Is a known principle for therapeutic "symptomatic" intervention, as it is required for patients with diseases mentioned in claims 30-32.

The present invention teaches that enhanced Tissue Factor expression does induce this process of blood vessel formation and/or wound healing. Also, other growth factors are known to be supportive in blood vessel formation and wound healing, mainly those known to be involved in the regulation of the physiological process. Ample examples in the literature show that different etiologies and mechanism that lead to impaired wound healing and/or Impaired vessel formation are of no rejuvance as long as the physiological process of blood vessel formation and/or wound healing can be induced by a method, *i. e.*, by a growth factor like VEGF or FGF. In other words; a growth factor (VEG F) known to induce therapeutic blood vessel formation in one disease does the same in other diseases. This is underlined by the ample use of VEGF and other growth factors in therapeutic angiogenesis by experts after the principle of the VEGF action was shown (*see* Brower (*Nature Biotechnology* (1999) 17:326-27)).

Knowing these uses of VEGF, the skilled artisan would expect, from reading the present specification, that upon therapeutic Tissue Factor expression, VEGF is also involved in the action as part of the process induced by Tissue Factor. This clearly confirms the claimed method of Tissue Factor Gene therapy targeting and

inducing the basic and general process of blood vessel formation and/or wound healing. Applicants also refer the Examiner to Semeraro *et al.*, (*Thromb. Haem.* (1997) 78:759-764), which summarize that Tissue Factor is expressed as an immediate early gene that via intracellular signal transduction triggers the production of growth factors. The invention teaches clearly and unambiguously that this triggering effect leads to blood vessel formation and/or wound healing which was new and could not be foreseen by experts.

Since the process is well described in animals and in humans, an the skilled artisan would know how to use Tissue Factor gene therapy in the therapeutic induction of this process. In addition, an expert demanding proof of principle or challenging this claim would certainly ask for an example of such a triggering effect in a model where blood vessel formation as well as wound healing is severely disturbed. This has been provided, since diabetic ulcerations are one of the most several states of disturbed blood vessel formation and/or wound healing, thus allowing prediction for less or equally severely disturbed conditions in which physiological induction of blood vessel formation and/or wound healing is missing.

Thus, Applicants submit that the specification, in combination with what was known in the art at the time the invention was filed, provides enablement for enhancing blood vessel formation in any location of the subject, or for treatment of diseases in human by any routes. Undue experimentation would not be required to create or practice the presently claimed invention. Thus, Applicants submit that this rejection has been obviated.

V. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 7-12, and 20-32 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite.

Claims 7-12 stand rejected under 35 U.S.C. § 112, second paragraph, as vague and indefinite because they purportedly fail to recite a positive step or conclusion, which clearly relates back to the preamble, and it is purportedly unclear how mere administration of TF relates to modulating blood vessel formation. Independent claim 7 has been amended to recite a conclusion which relates back to the preamble. With regard to how administration of TF relates to modulating blood vessel formation, Applicants respectfully submit that the present specification, especially on pages 3-6, as well as the Examples disclosed therein, describe in detail the relationship between TF and blood vessel formation. Thus, Applicants submit that this rejection has been obviated.

Claim 7 stands rejected under 35 U.S.C. § 112, second paragraph, as purportedly vague and indefinite for the recitation of "a fragment thereof". The specification purportedly fails to teach the lower limit for the nucleic acid fragment encoding the tissue factor, which maintains the function of the tissue factor. Applicants submit that the specification clearly discloses what is meant by "a fragment thereof". On page 3, lines 10-11, the specification describes the fragment of the tissue factor as "capable of forming vessels, in particular for wound healing". Thus, Applicants submit that the skilled artisan would know what is meant by "fragment" of tissue factor. Thus, Applicants submit that this rejection has been obviated.

Claims 13-17, and 20-32 stand rejected under 35 U.S.C. § 112, second paragraph, because although the claimed method provides for inducing local expression of tissue factor nucleic acid in said subject, it purportedly does not recite positive steps of the method. Applicants submit that independent claim 20 already recited a positive action step, *i.e.*, that of inducing the expression of the tissue factor nucleic acid. If the claims, read in light of the specification reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the courts can demand no more. Andrew Corp. v. Gabriel Electronics, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988). Applicants note that page 3, line 18 to page 4, line 6, describes in detail various methods of inducing the expression of the tissue factor nucleic acid. Thus, when read in light of the specification, the scope of the claims is clear. Applicants submit that this rejection has been obviated.

VI. REJECTIONS UNDER 35 U.S.C. § 102

Claims 7-10, 13-17, and 20-25 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by McDonald *et al.* (U.S. Patent No. 6,120,799).

Claim 7-10, 13-17, and 20-25 are drawn to a method of modulating blood vessel formation in subject comprising locally administering a functional tissue factor to a subject in need, wherein said TF or fragment thereof is administered in the form of an expressible nucleic acid.

McDonald *et al.* is cited for purportedly disclosing a method selectively targeting vascular endothelial cells by delivering cationic lipid and DNA complex to

vascular endothelial cells in a subject, wherein the complexes may comprise nucleotide constructs having promoters which are selectively and exclusively activated in the environment of a vascular endothelial cell, wherein the construct could encode a human tissue factor.

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." Jamesbury Corp. v. Litton Industrial Products, Inc. 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). The cited references do not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below.

McDonald *et al.* discloses "tissue factor" only in column 22, where tissue factors are described in connection with tumor vascularization. McDonald *et al.* teaches that tissue factor is involved in tumor growth inhibition by forming blood clots which cut off the oxygen and nutrient supplies to the tumor and cause tumor death. Thus McDoanald fails to disclose the treatment of normal tissues. The application of tissue factor as a DNA/cationic lipid complex to tumors cannot anticipate the therapeutic influencing of vessel formation in normal tissue of the claimed invention.

Thus, Applicants submit that this rejection is obviated.

VII. REJECTIONS UNDER 35 U.S.C. § 103

Claims 7-17 and 20-25 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over McDonald *et al.* (U.S. Patent No. 6,120,799) in further view of Dubensky *et al.* (*J. Virology* (1996) 70:508-19).

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re* Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the art cited by the Examiner, alone or in combination, does not suggest that the methods claimed, let alone that the claimed methods could be conducted with a reasonable expectation of success. In fact, the disclosure of McDonald *et al.* teaches away from the claims of the present invention.

The object of the presently claimed invention is to provide an agent which has a therapeutic influence on the vessel formation of normal tissues, especially for purposes of wound healing. In the present invention, this is achieved by inducing blood vessel formation by local expression of tissue factor nucleic acids (or local application of a functional tissue factor protein). This targeted induction of vessel formation in normal tissues is completely different from the random, untargeted formation of vessels in tumors. When the skilled artisan read McDonald *et al.*, they

would be dissuaded from using tissue factor to induce blood vessel formation, because McDonald *et al.* teaches that using tissue factor may induce tumor-like situations in normal tissue. Because of this, the skilled artisan would not have any expectation of success. It is not common practice in the art to transfer results from tumor experiments, as disclosed in McDonald *et al.*, to normal tissues, because tumorous tissues have lost their normal behavior.

Further, Applicants note that McDonald *et al.* assume rather than teach that Tissue Factor expression results in the death of vessels ("Another aspect of the invention which may be carried out using liposomes or nucleotide sequence/lipid complexes involves the formation of blood clots.... The present invention could achieve improved results using cationic lipids which lipids contain an agent which promotes the thrombogenic cascades"). Tissue Factor triggers several events, only one of which is coagulation, and McDonald *et al.* fails to address the right conditions where the pro-angiogenic activity of Tissue Factor is in favor of the pro-coagulant activity. Thus, the teachings of McDonald *et al.* disclose that pro-coagulatory activity, if occurring at all, is of no practical relevance although it might cause aide effects as it is (generally speaking) the case for many other pharmaceuticals for which beside the therapeutic action adverse action must be expected but can be minimized and handled clinically.

Dubensky fails to remedy the deficiencies of McDonald *et al.* because it merely discloses general methods for transporting substances into cells, including specific vectors for *in vitro* and *in vivo* transfer.

Thus, Applicants respectfully submit that this rejection is obviated.

Claims 7-10, 13-17, 20-25 and 28 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over McDonald *et al.* in further view of Sanford (U.S. Patent No. 5,100, 792).

The reasons why McDonald *et al.* fails to render the claimed invention obvious is discussed above. Sanford fails to remedy the deficiencies of McDonald *et al.* because it merely discloses general methods for transporting substances into cells, including specific vectors for *in vitro* and *in vivo* transfer.

Thus, Applicants submit that this rejection is obviated.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment and Reply

Marked-up Claims 7, 23-27, and 29

7. (Thrice Amended) A method of modulating blood vessel formation in a subject in need, comprising locally administering a functional tissue factor in a therapeutically effective amount to said subject in need, wherein said tissue factor or a fragment thereof is administered in the form of an expressible nucleic acid, and wherein the administration of the functional tissue factor modulates blood vessel formation.

23. (Amended) The method of claim [22] 20, wherein said nucleic acid is expressed transiently.

24. (Amended) The method of claim [22] 20, wherein said nucleic acid is a DNA.

25. (Amended) The method of claim [22] 20, wherein said nucleic acid is controlled by a constitutive or an inducible promoter.

26. (Amended) The method of claim [22] 20, wherein said nucleic acid is present in a Sindbis virus replicon vector.

27. (Amended) The method of claim [22] 20, wherein said nucleic acid is controlled by a CMV or SV40 promoter.

29. (Amended) The method of claim 7[,] or 20, [or 22] wherein said modulating is an activation of blood vessel formation.